Evolution of biomedical research during combat operations

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BACKGROUND: The implementation of a human research protection program in Afghanistan and the mobilization of the combat casualty research team have made it possible to design and efficiently conduct multifaceted, multisite, and prospective research studies in a combat environment. Still, to conduct research in such an environment, several unique challenges must be overcome.

METHODS: This article describes the development and conduct of three ongoing trauma-related biomedical research studies in Afghanistan, highlighting the challenges and lessons learned within the context of these studies.

RESULTS: Key challenges include the process of developing and getting approval for in-theater research protocols, the informed consent process, and logistics of conducting a biomedical research study in an austere environment. Despite these challenges, important lessons learned that can contribute to the success of a protocol include the need for clear operating procedures, judicious selection for which data points must be collected in-theater, and the importance anticipating the "fog and friction" of war.

CONCLUSION: As we continue the journey toward more sophisticated research capabilities in combat, this article will help inform the design and conduct of future research performed in a theater of war. Conducting biomedical research in a combat zone is an important but difficult element of military medicine. (*J Trauma Acute Care Surg*. 2013;75: S115–S119. Copyright © 2013 by Lippincott Williams & Wilkins)

KEY WORDS: Biomedical research; war; military personnel; wounds and injuries; research design.

Advances in medicine, particularly in the field of trauma, are accelerated during wartime.[1] Throughout history, military health care providers have repeatedly faced the unique challenges that come with caring for devastating combat casualties.[1,2] Many of these providers have dutifully embraced the practice of carefully documenting, analyzing, and communicating their experiences for the purpose of improving care and optimizing outcomes. Likewise, military health care providers caring for combat casualties in Iraq and Afghanistan during the last decade have continued this practice. One main difference, however, is that health care providers and investigators have more recently performed so within the context of an evolved clinical research regulatory landscape, influenced by the Belmont Report and other human subjects protection principles designed to protect the rights and welfare of subjects who participate in research.[3]

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In 2005, a military human research protection plan (HRPP) was drafted, which paved the way for conducting research in a combat environment and contributed to a paradigm shift in the types of studies that could be conducted.[3] Historically, research conducted in previous wars has largely consisted of retrospective and basic descriptive, observational, and survey studies. In Iraq and Afghanistan, these have been augmented by an increasing number of prospective noninterventional research protocols involving prospective data collection, recruitment of control subjects, and analysis of biologic specimens. Although common in the peacetime military and civilian settings, these types of studies present a vast number of challenges when attempted in a combat theater of operation. In addition, the evolution and mobilization of a combat causality research team is facilitating the oversight and conduct of research currently being conducted in the theater of war. Both of these factors are contributing to the conduct of more rigorous and robust research in a deployed setting.

The HRPP was implemented to provide human subjects protection oversight of all human subjects research conducted within the US Central Command (USCENTCOM) area of responsibility as an assured institution. US Army Medical Research and Materiel Command (MRMC) serves as the regulatory activities office that provides ethical review and regulatory oversight function for the USCENTCOM HRPP. This plan also mandates a human protections administrator in the area of responsibility and is responsible for the day-to-day operation and oversight of research activities and human subject protection issues.

The Joint Combat Casualty Research Team (JC2RT) is a USCENTCOM directed, forward deployed unit of military research scientists and clinicians tasked with overseeing,

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coordinating, facilitating, and conducting combat-relevant research in a deployed environment.[3,4] The JC2RT and the Joint Theater Trauma System have a separate but overlapping mission to improve combat casualty care that has been described elsewhere.[4] The first research team was conceived and deployed during combat operations in Iraq as the deployed combat casualty research team in mid 2005. Since then, there have been 12 teams deployed for this purpose with each team tour spanning 6 months; the most recent team is pictured in Figure 1. Over time, the composition of the team expanded to involve all three services. In 2010, as the operations tempo decreased in Iraq, the team transitioned its operations to Afghanistan where the team currently functions. The dynamic nature of the operational mission and varying research priorities at any given time has required that all teams prioritize and balance focus between all the phases of research.

Despite the implementation of the HRPP and the JC2RT, there are still inherent theater-specific considerations that influence the types of studies that are feasible in the combat setting, in particular, the high operational tempo, the changing mission and physical location of deployed units, a decreased length of deployment for physicians, the variable and uncertain level of security, and the absolute requirement that research should not interfere with operational missions, patient care, or force health protection. Despite these challenges and limitations, however, important and sophisticated research is currently being conducted in Afghanistan. In the remainder of this article, we will use three such studies, two investigating mild traumatic brain injury (mTBI) and one investigating hemorrhage and coagulopathy, to highlight some of the lessons learned in the conduct of research in a theater of war. A summary of these studies is included in Table 1. The purposes of this article were to give examples of ongoing, prospective biomedical research; describe the challenges faced in conducting human subject research in the deployed setting; and document important lessons learned in overcoming these obstacles.

mTBI Research

The large number of mTBI combat casualties caused by nonconventional warfare weapons such as improvised explosive devices has had a substantial impact on combat troop health and readiness. Therefore, mTBI has become a key priority in combat research. Research efforts have been concentrating on identifying and validating objective assessment tools with better specificity and sensitivity, including advanced brain imaging and serum biomarkers. The evaluation of objective assessment tools for mTBI in a deployment setting presents advantages for clinical management of mTBI and for determining feasibility of application in military medicine. Attempting to conduct such research during ongoing combat operations, while necessary, has come with unique challenges.

Figure 1. Joint combat casualty research team #12 in Kandahar, Afghanistan.

Magnetic resonance imaging (MRI) capabilities have recently become available at the main combat support hospitals in Afghanistan and have enabled clinical investigators to design and conduct the first prospective advanced brain MRI study ever attempted in a combat theater of operations. Conventional brain MRI, although more sensitive than computer tomography in detecting hemorrhage, edema, or ischemia in moderate-to-severe brain injuries, generally fails to detect clinically relevant abnormalities in acute mTBI.[5] Diffusion tensor imaging (DTI) is an advanced MRI technique that assesses the integrity of brain white matter and is thought to identify diffuse axonal injury, the hallmark of mTBI. DTI was found to be abnormal in blast-exposed service members who were medically evacuated from combat areas,[6] but little is known about more mildly injured service members who return to combat. This prospective observational study uses DTI, in the evaluation of subjects with acute blast-related mTBI. Nonconcussed volunteers who undergo the same imaging technique are enrolled as controls.

Biomarkers that reflect cellular damage in the brain are particularly intriguing as quantitative evaluation of reliable and specific biomarkers in serum would not only establish the presence of injury but also provide insight as to the nature and extent of the injury. Two potential biomarkers have been associated with brain injuries.[7] To evaluate the relations of these biomarkers specifically with mTBI, as opposed to the concomitant non–brain injury or other external brain stressors (e.g., sleep deprivation, combat stress, etc.), the deployment-based study examines serum concentrations of patients with recent concussion and of two control groups, namely, non-TBI injured controls and true noninjured controls. Thus, prospective enrollment into a three-cohort study is underway.

Hemorrhage Research

Throughout history, massive hemorrhage has been a major problem encountered by military physicians during wartime. It has been reported that during the last decade of combat operations in Iraq and Afghanistan, approximately 25% of patients are coagulopathic on admission.[8] Admission coagulopathy has an increased mortality (up to fourfold), worsening with increased injury severity and acidosis. Therefore, the identification of molecular mechanisms linking coagulopathy with immune inflammatory response to trauma has the potential to provide innovative new therapeutic approaches of damage-control resuscitation of military trauma casualties. As such, the first-ever observational study in Afghanistan involving prospective blood sample collection in US and non-US coalition forces

TABLE 1. Comparison of Three Complex Biomedical Research Studies Successfully Initiated in a Combat Setting

	DTI After mTBI	Biomarkers After mTBI	Hemorrhage
Primary investigator	LCDR Octavian Adam, US Navy	LCDR Walter Carr, US Navy	LTC Christopher White, US Army
Research Aims	Test an advanced MRI method of DTI in blast related mTBI military patients acutely after injury and correlate findings with mTBI-related short-term clinical outcomes	Evaluate serum biomarkers and QEEG for a mTBI cohort in a combat environment, for comparison with results for similar samples in civilian (noncombat) settings	Identify effects of damage-control resuscitation on the acute coagulopathy of trauma
Date approved	March 2012	March 2012	September 2011
Anticipated completion date (based on current enrollment rate)	September 2012	December 2012	December 2014
Target N	mTBI, 115; controls, 115	mTBI, 78; controls (non-TBI injury), 78; controls (noninjured) = 78	N = 300
Data/samples collected	Clinical data	Clinical data	Clinical data
	Neuropsychological tests	Quantitative electroencephalogram	In-theater research test (ROTEM)
	DTI (sent electronically to the United States)	Serum samples (shipped to United States)	Plasma samples (shipped to United States)
Data collection team	Local mTBI providers (Kandahar and Leatherneck)	Dedicated data collection team deployed in support of study (Bastion/Leatherneck)	JC2RT members (Bagram and Kandahar)

Information provided with permission from the primary investigators. QEEG, quantitative electroencephalography; ROTEM, rotational thromboelastometry.

within 24 hours of battle-related injury was designed and implemented at two sites.

CHALLENGES

Study Development

The process of developing a research study for implementation in a combat zone is fraught with challenges. Because of the frequent turnover of clinical staff and high operations tempo, it can be very difficult for clinicians to develop a protocol and complete all documents needed for institutional review board (IRB) review and approval, despite the assistance provided by JC2RT members. Alternatively, nondeployed researchers who do have time to devote to protocol development are not always familiar with the unique clinical and patient movement processes in a theater.

Although these challenges exist, the studies selected for inclusion in this article represent three different models by which studies can be successfully developed and conducted in a theater. The "DTI after mTBI" study was submitted by a principal investigator (PI) who was deployed as a clinician to Afghanistan. With the assistance of the JC2RT, he successfully submitted and navigated the protocol through the regulatory requirements to approval and, before redeploying, recruited a dedicated team of health care providers willing to execute the protocol in addition to their assigned clinical duties. The PI remained involved with the protocol and the in-theater research team, allowing the research study to successfully enroll the desired number of subjects. The second study, referred to as "biomarkers after mTBI" study was submitted by a stateside PI who then assembled a three member research team to deploy into theater for the entire duration it took to accrue the desired number of subjects. In this case, the JC2RT's main role was to assist the PI in solidifying the in-theater support and approvals before the study team's arrival in-theater. The last study, looking at hemorrhage and mechanisms of coagulopathy, was written and submitted by a stateside researcher who had returned from a deployment, but the study was executed in a theater by the JC2RT. While the success of an in-theater research study relies on many factors, each of these had dedicated professionals in the theater to champion the research.

Informed Consent

The Department of Defense is committed to the protection of subjects in research. The inability to obtain informed consent from severely battle-injured service members immediately after injury poses unique challenges in research in the deployed setting. The requirement to obtain informed consent can be waived in certain circumstances but only when the research poses no more than minimal risk to the subject and meets other regulatory requirements. For this reason, and because of the lack of availability of service member's legally authorized representatives to provide permission on their behalf, conduct of prospective interventional studies in the severely injured is prohibited.

For the biomarker study of mTBI, the investigative team, in coordination with the MRMC IRB, requested an alteration of the informed consent process to allow potential subjects with mTBI to evaluate their desire to participate and make an informed decision. Specifically, the research design was scripted such that when consent was requested of recently injured service members, the informed consent document was shortened to a single page commensurate with the isolated procedure and the potential for mental strain among subjects with mTBI. The remaining consenting process and data collection procedures

in the research design were scripted to occur approximately 24 hours following the initial encounter, allowing for a Department of Defense–mandated 24-hour rest period following injury. Any enrolled subject deciding against participation during the second request for consent is subsequently removed from the study.

For the hemorrhage study, a waiver of informed consent was requested owing to the minimal risk level of blood sample collection and the impracticability of consent immediately after severe injury due to incapacitation and chemical sedation. The waiver of informed consent was appropriately requested, considered, and ultimately approved by the IRB. However, after the enrollment of the first 12 patients, 25% of the patients were found to be awake at the 24-hour data collection point, despite their presenting critical injury. Thus, the study team coordinated with the IRB to develop a secondary verbal consent process in the event that the patient was determined by the medical staff to be awake, alert, and oriented to person, place, and time. Using a script, awake and alert participants are informed about the research study and asked if they were willing to continue participation in the study and if previous samples could be used.

Logistics

In all three studies, the practical and logistical aspect of prospective collection in the combat setting presented a challenge. In the case of the brain biomarker study, study team members maintain a physical presence at the hospital, as wireless communication (pagers or cellular telephones) are not available. Furthermore, physical separation between the concussive care clinic and the combat support hospital, where more than half the subjects are enrolled, necessitated at least two dedicated team members to successfully enroll subjects. Logistically, this has required a team member to be present at each site with required supplies to complete the enrollment and to conduct follow-up.

The "DTI after mTBI" study presented unique challenges related to the transmission of MRI data from theater to the United States. These challenges included electronic data size transfer limits and numerous intermediary relay servers requiring human troubleshooting and the maintenance of MRI equipment in the extreme environmental conditions of Afghanistan owing to heat and vibrations from aircraft traffic as well as ready availability of MRI technical support staff.

For the hemorrhage study, collecting samples from trauma patients, particularly during active resuscitation soon after injury, has required a tremendous amount of coordination so as to not interfere with active clinical care. In some cases, the patient was determined by the clinical staff to be too unstable to collect the additional sample. In these cases, the research team simply waited until the initial assessments were completed or until the patient had been stabilized. Occasionally, subjects were not enrolled because it simply was not possible to get the additional sample from the patient.

In the case of the hemorrhage study, the assistance of hospital laboratory staff members has been an integral part of the research process, providing space and expertise with processing and shipping samples. Additional support from the medical facility is also important, to ensure that adequate space and computer as well as telephone lines are available. Thus, the importance of an appropriate impact statement and proactive involvement and support of the local medical facility cannot be overstated.

Currently, samples are sent out of theater using commercial shipping companies from the designated base in Afghanistan to the study team within the United States, a process that takes approximately 3 days to 5 days. Individual samples are separated into two different shipments, to avoid a complete loss if there is an unanticipated delay in the shipment. To date, that has not been the case, but there has been a concerted effort to collaborate with the shipping companies with close tracking of the samples to ensure the most efficient route back to the United States. Establishing a close working relationship with the shipping company is an integral step and helps ensure shipments are coordinated, to include tracking and adding dry-ice to the shipping container, at the numerous destinations from the theater to the US laboratory.

Another challenge encountered with the current protocols is the availability of supplies and equipment needed to collect and process samples. With the austere environment (primarily heat and dust), a clear plan for maintenance of research equipment is essential. Owing to theater travel restrictions for vendor maintenance personnel, planning for replacement equipment to use while the original is sent home for repair is important. For rapidly consumed disposable supplies, it is important to project the demand well in advance and order supplies accordingly.

IMPORTANT LESSONS

As the team developed and implemented these studies, we encountered several potential crucial issues. Conducting research in an austere environment is challenging; however, with flexibility and teamwork, medical research with the potential for lasting impact on medical care can be successfully completed. There are several key lessons we would like to highlight for the conduct of future combat research, summarized in Table 2.

One important lesson learned relates to the critical importance of the development of a clear step-by-step standard operating procedure. This is particularly important because of the constant staff turnover and the fact that individuals other than the PI are often responsible for the execution of a study. Specific items to be addressed in a standard operating procedure include a clear delineation of the responsibilities of the onsite and the stateside study teams; information regarding the collection, processing, and shipment of samples; and the specific supportive roles the in-theater medical facility will be requested to fill.

Another lesson highlighted by these studies is the importance of keeping a research study as simple as possible, from the design of the study through to the data collection. The need for strict adherence to operational security, limited transportation at local sites, unpredictable travel between sites, unreliable communication systems, frequent power outages, changing security issues, and lack of supportive administrative staff make it imperative that research studies are carefully designed to address the scientific question as efficiently as possible. This includes minimizing, as much as possible, the collection of data by the in-theater study team. With the current use of electronic

TABLE 2. Recommendations for Successful Completion of Biomedical Research in Combat

Key Lesson Learned	Recommendations
Simplicity of study design	Minimize data collected in-theater
	Limit multiple data collection time points, if possible
	Consider ways to collect data with minimal burden on participants and in-theater research team
Development of standard operating procedures	Identify specific responsibilities of study team members both in-theater and at home station
	Specify specimen collection and processing steps
	Update procedures regularly as the environment changes
"Fog and friction" of war	Ensure good communication
	Create backup processes
	Incorporate additional time into project timeline
	Expect delays with the delivery of study equipment and supplies
	Anticipate minor protocol deviations and adjust accordingly

medical records and Web-based databases, much of the clinical data required in research studies can now be collected by study team members located in the United States. This allows the in-theater study team to focus attention on enrollment and the collection of information that is only available in-theater.

Lastly, a key lesson learned by our team is that the "fog and friction" of war, as coined by the military strategist Carl von Clausewitz,[9] is an important element to remember in any biomedical research accomplished in a combat theater. Unanticipated events and unexpected delays are frequent during all phases of the study. Despite this, it is important for the in-theater research team to accept some risk, particularly when enrolling the first few patients in a new research protocol. Remaining overly cautious has the potential to delay enrollment and the overall execution of the study, ultimately sabotaging relevant, high-impact research.

CONCLUSION

Conducting biomedical research in a combat theater is an important, but difficult, element of military medicine. With the successful implementation of a human research protection program, it is now possible to design and implement more complex and prospective research studies. However, because of the nature of a combat zone, there is a need to ensure that the appropriate regulatory processes are being followed, and the lessons learned from the experiences of the JC2RT in Afghanistan can provide a guide for future biomedical research projects. Within the context of research, observing and documenting vital lessons learned while caring for combat injured is an important legacy to military medicine.

AUTHORSHIP

J.J.H. contributed to the original conception of the article (with CT), wrote lessons learned, and coordinated contributions from other authors J.D.C. wrote the section on informed consent and waiver of informed consent M.P.D. wrote the section describing the research team and key portion of the lessons learned. G.D.C. wrote the section on describing the biomarker study and logistical challenges. J.J.D.L. wrote the section on the current science with respect to hemorrhage. T.B. critically revised the article and further developed the section on lessons learned. C.T. contributed to the original conception of the article (with J.J.H.), wrote the section on the development of the three different studies, and incorporated the final changes. R.T.R. composed the abstract and provided input on hemorrhage study discussion and challenges. S.A. wrote/contributed to the section discussing logistical challenges. K.K.C. wrote the background/introduction and integrated contributions from other authors. He also conducted critical review of and approved the final manuscript.

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DISCLOSURE

The authors declare no conflicts of interest.

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